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Short Communication

Phase II Study of Oxaliplatin in Poor-prognosis Non-small Cell Lung Cancer (NSCLC)

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The aim of this phase II study was to determine the antitumour activity and safety of *trans*-1-diaminocyclohexane-platinum (oxaliplatin) in previously untreated advanced non-small cell lung cancer (NSCLC) patients. 33 patients with unresectable and measurable NSCLC were entered into this phase II study between January 1992 and January 1994. Patients had either locoregional disease with performance status 2 (19 patients) or a stage IV disease (14 patients). Oxaliplatin (130 mg/m^2) was given on an out-patient basis (2-h infusion, every 21 days) without hydration. Response was assessed after every two courses. One hundred courses were administered, with a mean of three courses per patient (range 1–12). All patients were evaluable for response; 1 had a complete response, and 4 a partial response (overall response rate 15%, 95% confidence interval 5.1–31.9%). The median response duration was 5.9 months. All cycles ($n = 100$) were evaluable for toxicity assessment. Transient reversible, cold-related finger dysesthesias occurred in 29 patients, but were mild, and disappeared in most cases within a few days. We observed brief episodes of pharyngolaryngeal discomfort (8 patients, 11 episodes) accompanied in 4 cases (3 patients), by transient episodes of inspiratory stridor, leading 2 patients to treatment withdrawal. We conclude that oxaliplatin has activity in poor-prognosis NSCLC and that this treatment is feasible in out-patients; the absence of renal and haematological toxicity makes this drug a good candidate for further evaluation in NSCLC.

Key words: oxaliplatin chemotherapy, non-small cell lung cancer
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INTRODUCTION

THE ROLE of platinum-based chemotherapy in advanced non-small cell lung cancer (NSCLC) has been demonstrated by a recent meta-analysis [1]. The use of cisplatin is limited by cumulative nephrotoxicity, neurotoxicity and high and prolonged emetic potential. Other less toxic platinum analogues have been tested. Oxaliplatin, a diaminocyclohexane-platinum complex, has shown *in vitro* and *in vivo* antitumoral activity, having no or incomplete cross-resistance with other platinum derivatives [2]. In phase I clinical trials, the safety profile of oxaliplatin was characterised by cumulative, dose-related and reversible peripheral sensory neuropathy as the dose limiting toxicity, mild gastrointestinal toxicity, and minimal haematotoxicity, in the absence of nephrotoxicity and ototoxicity; the recommended dose is 130 mg/m^2 by short intravenous infusion repeated every 3 weeks [3–5]. Oxaliplatin is active in first and second line treatment of advanced colorectal carcinoma [6–8] and has been recently registered for this indication in France. Phase II studies are in progress in ovarian cancer, non-Hodgkin's lymphomas and squamous cell carcinoma of head and neck [9–11]. We present the first single-agent phase II study with oxaliplatin in patients with unresectable NSCLC and poor prognostic factors. Our aim was to assess, in a preliminary study, the activity of oxaliplatin in NSCLC.

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PATIENTS AND METHODS

Eligibility was restricted to patients with locoregional disease but poor performance status (PS, WHO 2) or with stage IV disease. Other inclusion criteria were histological proof of NSCLC, unresectable tumour for oncological or functional reasons, measurable disease on computed tomography (CT) scan, age under 75 years, granulocyte count $\geq 2000/mm^3$, platelet count $\geq 125\,000/mm^3$ and no previous chemotherapy. The protocol was approved by the local Ethical Committee and all patients gave written informed consent.

Oxaliplatin was administered at a dose of $130\,mg/m^2$, as a 2-h intravenous infusion every 21 days on an out-patient basis. A single dose of 5-hydroxytryptamine 3 (5-HT3) antagonists, ondansetron or granisetron, was given as antiemetic medication and no previous hydration was necessary.

Pretherapeutic staging consisted of full history, clinical examination, chest roentgenogram and chest CT scan, bronchoscopy with biopsy, brain and abdomen CT scan, radionuclide bone scan, electrocardiogram, blood counts and standard laboratory parameters. During the study, a 3-weekly evaluation was performed before each chemotherapy cycle, including physical examination, determination of changes in PS, assessment of all toxicities observed after the previous course, chest X-ray, and routine haematological and biochemical parameters. There was no systematic complete blood cell counts between the courses.

Toxicity was graded by WHO criteria except for neurological toxicity. The peripheral neurological toxicities were graded according to a specific scale described elsewhere [6]: grade I, peripheral paresthesias of moderate intensity for less than 7 days; grade II, peripheral paresthesias of moderate intensity lasting 7–21 days; grade III, incomplete recovery between courses or mild hypoesthesia of the finger tips or foot plants; grade IV, permanent functional impairment. Dose modification was planned only in case of grade II–IV toxicities: dose reduction of 25% in the case of grade III neutropenia or thrombopenia, interruption of the treatment in the case of grade IV neutropenia or thrombopenia, except if there was an objective response (dose reduction of 50% after complete recuperation); interruption of the treatment in the case of grade III–IV peripheral neuropathy and ototoxicity; dose reduction of 25% in the case of grade II nephrotoxicity, of 50% in the case of grade III nephrotoxicity, and interruption of the treatment in the case of grade IV nephrotoxicity.

The response to treatment was assessed after two courses, according to WHO criteria. Bone metastases were not considered evaluable for response. In the case of objective response or stable disease, chemotherapy was continued with the usual 3-weekly evaluation by chest X-ray. In the absence of progression, four additional courses were given before a new complete evaluation of response. Thereafter, treatment was continued until progression of the disease. In the case of progression, even after the first cycle, oxaliplatin was stopped. Responses were assessed by an external review panel, including a radiologist.

The duration of response was determined as the interval between the start of treatment and progression of disease. The duration of survival was measured from the start of chemotherapy to death or last follow-up visit. Survival curves were obtained using the Kaplan–Meier method.

Table 1. *Patient characteristics*

Characteristics	Number of patients (%)
Males:female	29:4 (88:12)
Performance status	
0–1	9 (27)
2	24 (73)
Pathological subtype	
Squamous	20 (61)
Adenocarcinoma	5 (15)
Large cell	8 (24)
TNM staging	
Stage I	5 (15)
Stage IIIA	5 (15)
Stage IIIB	9 (28)
Stage IV	14 (42)
Number of metastatic sites (14 patients)	
1	9 (64)
2	4 (29)
3 or more	1 (7)
Metastatic sites	
Bone	7 (50)
Liver	3 (21)
Adrenal (s)	4 (29)
Others	7 (50)

RESULTS

Between January 1992 and January 1994, 33 patients (mean age 67 ± 5.6 years) with unresectable NSCLC were entered into the study (Table 1). Patients had either poor PS (WHO 2) with locoregional disease (19 of 33 patients) or stage IV disease (14 of 33 patients). One hundred courses were administered, with a mean of three courses per patient (range 1–12). There were no dose reductions. Five cycles were delayed for either intercurrent pneumonia ($n = 1$), brief grade 2 neutropenia ($n = 1$), or miscellaneous non-toxic reasons ($n = 3$). The given oxaliplatin dose intensity was 98% of the planned dose.

Toxicity

All cycles were evaluable for toxicity (Table 2). Neurotoxicity was the most frequent toxicity. A peripheral purely sensory neurological syndrome was observed in 29 patients (88%) and 86 cycles (86%): transient dysesthesia of fingers, toes and sometimes lips and nose appeared early after the end of the infusion and were induced or exacerbated by cold. No

Table 2. *Maximum toxicity in* 33 *assessable patients during the total treatment period (*100 *cycles): numbers (percentage) of patients*

	Grade (WHO criteria)			
	I	II	III	IV
Neutropenia*†	1 (3)	1 (3)	0 (0)	0 (0)
Thrombopenia*†	0 (0)	0 (0)	0 (0)	0 (0)
Anaemia*†	2 (6)	0 (0)	0 (0)	0 (0)
Mucositis*	1 (3)	0 (0)	0 (0)	0 (0)
Diarrhoea*	1 (3)	0 (0)	0 (0)	0 (0)
Nausea–vomiting*	8 (24)	8 (24)	0 (0)	0 (0)
Peripheral neuropathy‡	4 (12)	21 (64)	4 (12)	0 (0)
Renal*	0 (0)	0 (0)	0 (0)	0 (0)

*WHO criteria, except for peripheral neuropathy. †Evaluated at day 21. ‡Grade I, peripheral paresthesias present less than 7 days; grade II, more than 7 days and less than 21 days; grade III, permanent dysaesthesia; grade IV, permanent severe functional impairment.

motor involvement was observed. In the 4 patients with grade 3 (specific scale) neurotoxicity, the treatment had to be stopped, and the dysesthesia disappeared after 1, 1, 6 and 12 months. The most remarkable side-effects were acute episodes of pharyngolaryngeal discomfort occurring shortly after the end of the treatment administration, of short duration, and often induced by cold drinks. In most cases, symptoms were limited to transient pharyngolaryngeal dysesthesias with a subjective tightening feeling (5 patients, seven episodes), however, 3 other patients had a more disquieting syndrome, with an observable inspiratory stridor, leading to hospitalisation (four episodes), and to treatment withdrawal in 2 patients. Laryngeal endoscopic examination, performed during one of those episodes, failed to disclose any abnormality. There was no significant haematological or renal toxicity. When nausea and vomiting were present, they were short in duration and mild in intensity. Tinnitus was unusual (2 patients, 6%). No toxic death was observed.

Response

The 33 eligible patients were evaluable for response. Table 3 lists the response data according to patient characteristics. 5 patients had an objective response (overall response rate 15%, 95% confidence interval 5.1–31.9%). There was 1 complete response, in a stage IV patient; this patient presented with a squamous cell carcinoma and an adrenal metastasis. The median duration of response was 5.9 months. 2 other patients had a minor response (− 41 and − 34% reduction in measurable disease, lasting 4.7 and 4.8 months). 12 patients remained stable (36%) and progression was observed in 16 patients (48%). Median survival was 8.03 months for all patients, and 17.1 months for the 5 responders. At the date of analysis, 31 of the 33 patients were dead, 1 patient was lost to follow-up in progression at 5.8 months, 1 patient was still in complete response at 50 months.

DISCUSSION

In the present study, we determined that oxaliplatin has some activity in NSCLC, in a population with a large proportion of patients with poor PS. The response rate of 15% was lower than that observed with taxanes, camptothecin, gemcitabine and vinorelbine [12], but is near the reported response rate of cisplatin [13] and higher than that of carboplatin [14].

The more frequently observed side-effect was the previously described acute peripheral sensory neuropathy. The absence of cumulative neurological complications was probably explained by the low individual number of cycles. The likelihood of developing at least moderate functional impairment or lasting (more than 21 days) dysesthesias rises with cumulative dose and becomes 50% at doses superior to 1170 mg/m^2 whatever the infusion modality [5–7, 12]. When tissue specimens were analysed for pathological examination, the features of the oxaliplatin-induced neuropathy were consistent with damage of small amyelic fibres, rather than large sensory fibre injury with axonal degeneration and segmental demyelination observed with cisplatin-induced neurotoxicity [15].

The pharyngolaryngeal manifestations observed in the present study and the acute neurosensory symptoms shared common features: they often occurred together, early after oxaliplatin infusion, could be limited to transient dysesthesias (of pharyngeal area, and fingers), and were cold related. These common features suggest a common mechanism. Episodes of pharyngolaryngeal dysesthesias were observed during phase I trials, where oxaliplatin was given by short infusions [3], but were seldom described in other studies of patients with colorectal carcinoma treated by continuous infusion [5–7]. These data suggest that these phenomena are probably schedule-dependant and could be prevented by longer infusions. Differences in the study populations, for example, a high incidence of chronic laryngitis among patients with lung cancer and past smoking history, could also account for the relatively high incidence of pharyngolaryngeal discomfort in the present series.

In conclusion, chemotherapy with oxaliplatin has significant activity in NSCLC even for patients in poor general condition, and offers perspectives of preserving quality of life. This response rate, obtained in spite of poor prognostic factors and in the absence of haematological or renal toxicities, compares favourably with other platinium analogues and opens perspectives of dose escalations and of associations in multi-agent regimens.

Table 3. Response rate in 33 evaluable patients: numbers (percentage) of patients in each group

Response	Complete response	Partial response	No change	Progression
All patients ($n = 33$)	1 (3)	4 (12)	12 (36)	16 (48)
Stages				
I–IIIb ($n = 19$)	0 (0)	3 (16)	10 (53)	6 (32)
IV ($n = 14$)	1 (7)	1 (7)	2 (14)	10 (71)
Pathology				
Squamous ($n = 20$)	1 (5)	2 (10)	9 (45)	8 (40)
Adenocarcinoma ($n = 5$)	0 (0)	0 (0)	2 (40)	3 (60)
Large cell ($n = 8$)	0 (0)	2 (25)	1 (12.5)	5 (62.5)

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